REMARKS

This paper is a Response to the Office Action mailed July 31, 2009. Claims 111 to 116, 120 to 130, 133 and 134 are under consideration.

Regarding the Claim Amendments

The amendment to the claims were made to address informalities. In particular, the amendment to claim 112 to recite "antigen binding" instead of "functional fragment" was made to provide improved antecedent basis for this term. Thus, as the claim amendment was made to address an informality, no new matter has been added and entry thereof is respectfully requested.

Regarding the Priority Application

Applicants respectfully do not concede the issue of priority. Applicants maintain that for the reasons of record the claims are adequately supported as of the July 4 or 6, 2002 priority application filing dates.

In terms of the new assertion that claims directed to the antibody or hybridoma are not supported prior to July 2, 2003, Applicants disagree. First, PM-2 light and heavy chain variable region sequences, set forth as SEQ ID NOs: 5 and 7, respectively, are disclosed in the earlier filed priority application, namely DE 102 30 516, filed July 6, 2002. Consequently, claims directed to antibodies and binding fragments comprising light and heavy chain variable region sequences (SEQ ID NOs: 5 and 7), and any cell line, including hybridoma cell lines, that produces antibodies and binding fragments comprising heavy and light chain variable region sequences (SEQ ID NOs: 5 and 7) are clearly adequately supported at least as of July 6, 2002.

Second, in order for a claim to be adequately supported under 35 U.S.C. §112, first paragraph, there is no requirement that the claimed subject matter be "publicly available." To the extent that the Examiner maintains that being "publicly available" is required, Applicants respectfully request that the Examiner cite competent statutory or other authority that states that support under 35 U.S.C. §112, first paragraph, requires the claimed subject matter to be "publicly available."

I. REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The rejection of claims 111 to 116 and 120 to 130 under 35 U.S.C. §112, second paragraph, as allegedly indefinite is respectfully traversed. The grounds for rejection are set forth in the Office Action, pages 3-4.

The claims are clear and definite under 35 U.S.C. §112, second paragraph. Claim 112 has been amended to recite "antigen binding" instead of "functional" fragment. In view of the amendment, the ground for rejection is moot.

In terms of the reference to the term "epitope," the first instance of a noun used in a claim is typically preceded by the indefinite article "a" or "an," such as "an" epitope. The second and subsequent instances of the same noun used in a claim is conventionally referred to by the terms "the" or "said," such as "said" epitope. Here, in claim 111 the first instance of "epitope" in line 3 is preceded by the term "an" and the second instance of "epitope" in line 7 is preceded by the term "said." Consequently, the second instance of "said epitope" in claim 1, line 7, refers to the epitope referred to in the first instance in claim 1, line 3, namely "an epitope," and therefore adequate antecedent basis for the term epitope in line 9 is provided. Accordingly, claims 111 to 116 and 120 to 130 are limited to antibodies and antigen binding fragments that specifically bind to the epitope that the PM-2 antibody specifically binds and, therefore, are clear and definite under 35 U.S.C. §112, second paragraph. In view of the foregoing, claims 111 to 116 and 120 to 130 are clear and definite under 35 U.S.C. §112, second paragraph. Accordingly, the rejection must be withdrawn.

II. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The rejection of claims 111 to 116, 120 to 130 and 134 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement is respectfully traversed. The grounds for rejection are set forth in the Office Action, pages 4-15.

Regarding the ground for rejection due to the deposit of DSM ACC2600 in the specification allegedly being made after the effective filing date, Applicants respectfully point out that the effective filing date of the application is the filing date of the international application, namely PCT/IB2003/003487, which is July 2, 2003, and is not the July 4, 2002 filing date of the earlier filed German priority application. The international application includes a specific reference to the deposited biological material, namely DSM ACC2600, and date of the deposit. Consequently, the deposit was not made after the effective filing

date, and therefore, a verified statement that the deposited material is the same as that identified in the specification is not required.

Turning to the rejection due to the claims allegedly encompassing "a genus of antibodies binding to a genus of unknown epitopes on unknown proteins," the claims are directed to antibodies and antigen binding fragments that specifically bind to the epitope that the PM-2 antibody specifically binds. Accordingly, the claimed antibodies and antigen binding fragments bind to the epitope that the PM-2 antibody binds the claimed antibodies bind to a single epitope, and do not bind to a "a genus of epitopes." Consequently, the alleged basis for rejection due to the antibodies and fragments allegedly binding to a genus of epitopes (e.g., pages 7, 9 and 10, and the cited Coleman, Abaza et al. and Burgess et al. references) is inapplicable to the claims.

In terms of the rejection based upon the Pero et al. publication (US 2003/0105000) cited at page 9 of the Action, this reference describes differences in binding of SH2 containing Grb14 proteins to another protein (ErbB2) and peptide-phage sequences, not binding between antibodies and antigens. Thus, Pero et al. describes interactions between other proteins that are unrelated to antibody-antigen interactions. Furthermore, as discussed above Applicants' claims are not directed to variant antigen sequences in the sense that the antibodies and antigen binding fragments bind to different antigens having different epitopes. Consequently, the Pero et al. publication (US 2003/0105000) is irrelevant to whether or not the claimed antibodies and antigen binding fragments are adequately enabled under 35 U.S.C. §112, first paragraph.

In terms of the rejection at page 10 and pages 11-14 of the Action allegedly due to "one of skill in the art cannot predictably expect that this genus of antibodies will....bind to other cancer cell types" or that "expression of proteins in cultured cell lines is not predictably indicative of the proteins expression *in vivo* because of artifacts associated with cultured cells *in vitro*, and the heterogeneity of cancer," Applicants need not enable what is not claimed and claims 111 to 116, 120 to 125, 127 to 130 and 134 recite binding to at least one of two well defined cell lines, namely ASPC-1 (ATCC Accession No. CRL-1682), or BXPC-3 (ATCC Accession No. CRL-1687). Thus, because claims 111 to 116, 120 to 125, 127 to 130 and 134 do not require that the antibodies "bind to other cancer cell types" or bind to various cancer cells *in vivo* this ground for rejection is irrelevant to enablement of claims 111 to 116, 120 to 125, 127 to 130 and 134.

In terms of claim 126, which recites that the claimed antibodies or antigen binding fragments bind to certain adenocarcinomas or carcinomas, one of skill in the art could readily identify antibodies and antigen binding fragments that bind to the adenocarcinomas or carcinomas, without undue experimentation. In this regard, the specification discloses methods for assaying antibody binding using IHC staining of cryosections of human tumors (page 46, line 25, to page 47, line 10). The specification discloses that using this assay revealed that PM-2 reacted with a large number of carcinomas and adenocarcinomas (page 53, lines 22-25, and page 54, Table 4). Thus, in view of the guidance in the specification which discloses a routine screen to determine antibody binding one of skill in the art could readily identify antibodies and antigen binding fragments that bind to any of the recited adenocarcinomas and carcinomas in claim 126 without undue experimentation.

In terms of the ground for rejection at the paragraph bridging pages 10 and 11 of the Action allegedly due to antibodies being cytotoxic towards some cell lines but not others, Applicants need not enable what is not claimed and claims 111 to 116, 120 to 126, 130 and 134 do not require cell cytotoxicity. Thus, the grounds for rejection due to absence of cytoxoicity against a given cell line is irrelevant to enablement of claims 111 to 116, 120 to 126, 130 and 134.

In terms of claims 127 to 129, which recite that the claimed antibodies or antigen binding fragments "inhibit proliferation" or "induce apoptosis" of BXPC-3 or adenocarcinoma cells of the pancreas, one of skill in the art could readily identify antibodies and antigen binding fragments that inhibit proliferation or induce apoptosis of BXPC-3 or adenocarcinoma cells of the pancreas without undue experimentation. In this regard, the specification discloses methods for ascertaining antibody induction of apoptosis and inhibition of cell proliferation (Examples 4 and 5, respectively). The specification discloses that these assays revealed that PM-2 induced apoptosis and inhibited cell proliferation of BXPC-3 cell line (page 56, lines 8-29, and page 57, line 28, to page 58, line 30). Thus, one of skill in the art, in view of the guidance in the specification could readily identify any antibody or antigen binding fragment in claims 127 to 129 that inhibits proliferation or induces apoptosis using a routine screen and without undue experimentation.

Applicants respectfully remind the Patent Office that the proper standard for enablement under 35 U.S.C. §112, is whether one skilled in the art could make and use the invention without undue experimentation. In this regard, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question

provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands* 858 F.2d 731, 737 (Fed. Cir. 1988) In view of the guidance in the specification and knowledge and skill in the art at the time of the invention variants of antibodies and antigen binding fragments having the requisite activity could be made and used without undue experimentation using routine methods disclosed in the specification or that were known in the art at the time of the invention.

Claims 111 to 116, 120 to 130 and 134 are analogous to *Wands*, where the court held that screening hybridomas to determine those that produced monoclonal antibodies having a particular binding characteristic did not require undue experimentation. Likewise, undue experimentation would not be required to make and identify variant antibodies and antigen binding fragments that bind to an epitope of a polypeptide expressed by at least one of the recited cell lines, to which epitope PM-2 antibody binds, given that 1) producing antibody variants and fragments was routine in the art at the time of the invention; and 2) binding assays are disclosed in the specification and other antibody binding assays were known in the art at the time of the invention. Thus, there is no need for the skilled artisan to "predict" antibody or binding fragment variants that bind to the epitope of the polypeptide to which PM-2 antibody binds because making antibodies and fragments and identifying those that bind, induce apoptosis or inhibit cell proliferation would not require undue experimentation in view of the guidance in the specification and knowledge in the art at the time of the invention.

Consequently, the statements in the Office Action (e.g., pages 10, 11, 13 and 14) that purportedly support the rejection, namely that allegedly one of skill in the art "cannot predictably expect that the genus of antibodies will induce apoptosis of BXPC-3 cells or pancreatic adenocarcinoma cells" or allegedly "the unpredictability of correlating the activities of an antibody with its binding to an epitope or protein" or that allegedly "no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed," are irrelevant to enablement of the claims since there is no need to predict the effect of any amino acid change in order to make and identify antibodies and antigen binding fragments having the recited activities without undue experimentation.

In support of Applicants' position, claims directed to a genus of antibodies where no antibody has ever been produced are routinely granted by the Patent Office. Thus, if claims directed to a genus of antibodies have been granted where no antibody has even been made

and therefore where no antibody sequences are even known, surely knowledge of antibody sequence or prediction of the effects of particular amino acid variations on binding is not required to satisfy the enablement requirement under 35 U.S.C. §112. Consequently, it is clear that enablement of the claims under 35 U.S.C. §112 does not require knowledge of antibody sequence or predicting the effects of particular sequence variations on antibody binding or activity. Thus, the repeated statements by the Patent Office that one would have to predict the effect of changes in antibody sequence on binding or activity clearly indicates that the Patent Office is applying an incorrect enablement standard to the claims.

Furthermore, Applicants point out that the Patent Office cannot insist that the specification enable the claims by a particular methodology, namely predicting antibody variants that would bind or have another activity. In this regard, there is no authority requiring Applicant to demonstrate enablement by a particular methodology selected by the Patent Office to the exclusion of other methodologies. Consequently, for the Patent Office to demand that Applicant demonstrate enablement by a particular methodology under 35 U.S.C. §112, first paragraph, is clearly improper.

Here, the level of knowledge and skill in the art regarding making antibodies and antigen binding fragments thereof was high. For example, methods of producing antibodies and variants without undue experimentation are disclosed in the specification (page 24, line 5, to page 28, line 24). Methods of producing antibody fragments (*e.g.*, Fv, Fab, Fab' and $F(ab')_2$) were known in the art and were routine at the time of the invention. Thus, in view of the guidance in the specification and the high level of knowledge and skill in the art at the time of the invention, one skilled in the art could readily make antibodies and antigen binding fragments without undue experimentation.

Second, methods of identifying antibodies and fragments that bind antigen without undue experimentation are also taught by the specification. In particular, routine methods for measuring antibody binding to antigen or cell lines, as well as methods for measuring cell proliferation and apoptosis are disclosed in the specification (page 14, lines 9-27; page 45, line 24 to page 47, line 10; page 47, line 27, to page 49, line 14; page 56, lines 1-27; and page 57, line 19, to page 58, line 11). Thus, antibodies and binding fragments that bind to an epitope of a polypeptide expressed by at least one of ASPC-1 (ATCC Accession No. CRL-1682), or BXPC-3 (ATCC Accession No. CRL-1687) cells, to which epitope PM-2 antibody produced by a cell line deposited as DSM ACC 2600 binds, as well as such antibodies and

antigen binding fragments that additionally inhibit cell proliferation or induce apoptosis, could be identified without undue experimentation at the time of the invention.

For example, if one skilled in the art wanted to produce antibodies or antigen binding fragments that specifically bind to an epitope of a polypeptide expressed by at least one of ASPC-1 (ATCC Accession No. CRL-1682), or BXPC-3 (ATCC Accession No. CRL-1687) cells, to which epitope PM-2 antibody produced by a cell line deposited as DSM ACC 2600 also binds, the skilled artisan could simply introduce mutations in a light and/or heavy chain variable region sequence (SEQ ID NOs:5 or 7) and then verify those that bind to the epitope to which PM-2 binds, for example, by a competition binding assay with PM-2 antibody for binding to ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cells. A particular example of the routine nature of methods of producing and identifying variant antibodies having binding activity at the time of the invention is submitted herewith as Exhibit E (Boder *et al.*, Proc. Nat'l Acad. Sci. USA 97:10701 (2000)). The authors of Exhibit E describe directed evolution of scFv fragments, and generation of a large number of Fv sequences with improved binding affinity compared to non-mutagenized antibody. Notably, the authors remarked upon "[t]he relative ease with which extremely high affinity has been attained in this study." (page 10705, first column, last full paragraph) Consequently, in view of the fact that variants with improved affinity could be made "with relative ease" at the time of the invention, one of skill in the art clearly would have been able to produce variant antibodies and fragments having binding affinity without any need to predict in advance the effect of any amino acid variation without undue experimentation at the time of the invention.

In sum, analogous to *In re Wands* where the court held that identifying hybridomas that have a particular binding characteristic did not require undue experimentation, making and identifying the claimed antibodies and antigen binding fragments would not require undue experimentation, given that 1) producing antibodies and fragments was routine in the art at the time of the invention; and 2) routine cell binding, antibody competition and cell proliferation/apoptosis assays are disclosed in the specification and were known in the art at the time of the invention. Consequently, contrary to the statements in the Office Action where the Examiner alleges that one skilled in the art would have to "predict" the effect of sequence changes on binding, inhibition of cell proliferation or induce apoptosis, there is no actual need for the skilled artisan to "predict" variants or fragments that bind to the recited polypeptide, inhibit cell proliferation or induce apoptosis, in order to make variants and

antigen binding fragments because making and identifying antibodies and antigen fragments having the requisite binding, inhibition of cell proliferation or induction of apoptosis was routine at the time of the invention.

Thus, in view of the high level of knowledge and skill in the art at the time of the invention clearly the skilled artisan could make antibodies and fragments and identify those that bind in view of the guidance in the specification and knowledge in the art at the time of the invention without undue experimentation. Consequently, the claims are adequately enabled under 35 U.S.C. §112, first paragraph, and the rejection must be withdrawn.

In addition to the fact that one skilled in the art could make and identify antibodies and fragments at the time of the invention without undue experimentation, the level of knowledge and skill with respect to antibody structure and function at the time of the invention was high. For example, the role of antibody heavy and light chain variable regions, particularly CDRs and FRs, in antigen binding was well understood by the skilled artisan at the time of the invention. The specification also discloses the role of heavy and light chain variable regions, including CDRs, in binding activity (page 22, line 6, to page 23, line 2), and the predicted location and sequences of CDRs in SEQ ID NOs:5 and 7 (see, e.g., Figures 14 and 15; page 5, lines 7-8; and page 50, lines 14-19). In view of the fact that the predicted locations of all 6 CDRs are taught by the specification, the skilled artisan would also know the locations of all FRs in SEQ ID NOs:5 and 7.

In view of the high level of knowledge and skill in the art at the time of the invention and the guidance in the specification clearly the skilled artisan would be apprised of antibody regions and amino acid sequences that participate in binding. Thus, one of skill in the art would have known regions of SEQ ID NOs:5 and 7 more or less amenable to substitution. Consequently, even if for the sake of argument the skilled artisan wanted to choose particular amino acid residues to vary (even though such *a priori* selection is not required to make the claimed antibodies and fragments without undue experimentation as discussed in detail above, nor is such selection required to satisfy enablement under 35 U.S.C. §112, first paragraph, in view of the extensive knowledge in the art), the skilled artisan could indeed select variants with a high probability of having at least partial binding activity.

To further corroborate that one of skill in the art could produce antibodies and fragments having at least some detectable antigen binding affinity, inhibit cell proliferation or induce apoptosis without undue experimentation at the time of the invention, submitted herewith is a Declaration under 37 C.F.R. §1.132, executed by Dr. Peter Vollmers. As stated

in the Declaration, Dr. Vollmers, based upon objective facts and conclusions based upon the objective facts, concludes that one of skill in the art, in view of the guidance in the specification and knowledge in the art at the time of the invention, could produce antibodies and functional fragments having binding activity without undue experimentation (Paragraph 20). The facts and Dr. Vollmers' conclusions based upon the facts are summarized in the Declaration, Paragraphs 20-24. Accordingly, the Declaration under 37C.F.R. §1.132, executed by Dr. Peter Vollmers corroborates that one of skill in the art could produce variant antibodies and functional fragments having binding affinity, inhibit cell proliferation or induce apoptosis, without undue experimentation at the time of the invention.

In sum, given the fact that one skilled in the art could make and identify variant antibodies and fragments that bind to an epitope of a polypeptide expressed by at least one ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cells to which PM-2 antibody produced by a cell line deposited as DSM ACC 2600 also binds without undue experimentation at the time of the invention, there is no need to predict the effect of variations on antibody binding. In addition, the Patent Office cannot properly demand that Applicants demonstrate enablement of the claims by a particular methodology to satisfy 35 U.S.C. §112, first paragraph, i.e., be able to predict variants. Here, one skilled in the art is not required to predict the effect of any change in order to make and identify antibodies and fragments that bind, inhibit proliferation or induce apoptosis without undue experimentation, as held by the court in *Wands*, and corroborated by Exhibit E and the Declaration under 37C.F.R. §1.132, executed by Dr. Peter Vollmers. Consequently, the claims are adequately enabled under 35 U.S.C. §112, first paragraph, and Applicants respectfully request withdrawal of the rejection.

WRITTEN DESCRIPTION

The rejection of claims 111 to 116 and 120 to 130 under 35 U.S.C. §112, first paragraph, as allegedly lacking an adequate written description is respectfully traversed. The grounds for rejection are set forth in the Office Action, pages 15-22.

Claims 111 to 116 and 120 to 130 prior to entry of this paper are adequately described.

In terms of the grounds for rejection due to the claims allegedly encompassing "a genus of antibodies binding to unknown epitopes on unknown proteins," the claims are directed to antibodies and antigen binding fragments that specifically bind to the epitope that the PM-2 antibody specifically binds. Accordingly, as the claimed antibodies and antigen

binding fragments bind to the epitope that the PM-2 antibody binds the claimed antibodies bind to a single epitope, and do not bind to a "a genus of epitopes" Consequently, the ground for rejection due to the antibodies and fragments allegedly binding to a genus of epitopes is inapplicable to the claims.

Second, with respect to the statement at page 16 of the Action, namely allegedly that "there is a lack predictable structure function correlation between the structure of antibody....and binding to its antigen or epitope within the antigen," Applicants respectfully disagree. In this regard, the Rudikoff et al. article cited by the Patent Office and presumably relied upon was published in 1979, which was more than 20 years prior to the 2002 filing date of the priority applications. Thus, clearly the Rudikoff et al. article fails to accurately represent the knowledge in the antibody art at the time of the invention.

Further in this regard, in *Enzo V. Gen-Probe, Inc.*, 323 F.3d 956 (Fed. Cir. 2002) "*Enzo II*" the Federal Circuit offered an example of a claim that the PTO would find in compliance with §112, first paragraph, defined by functional characteristics, namely "an isolated antibody capable of binding to antigen X....in light of the well defined structural characteristics of the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature." Thus, under *Enzo II,* antibodies are adequately described under 35 U.S.C. §112, first paragraph, solely in terms of functional characteristics since the structural characteristics of antibodies are well known and are coupled with the functional characteristic of binding. Consequently, the written description requirement with respect to a genus of antibodies and binding fragments can be satisfied, as it is here, given the sufficient relevant identifying functional characteristics and the correlation between structure and function, even if the antigen has not been fully characterized.

Here, as discussed in detail in the record and below, the claimed antibodies and binding fragments are defined structurally and functionally. Thus, the claims clearly meet the standard set forth by the court in *Enzo II*, as corroborated by the more recent decision in *Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052 (Fed. Cir. 2005), and are in contrast to the facts in *Enzo V. Gen-Probe, Inc.*, 296 F.3d 1316 (Fed. Cir. 2002) since the antibodies and binding fragments are not defined "solely by its principal biological property."

Third, with respect to the statement at page 17 of the Action that affinity of the first humanized antibody was CAMPATH1 was nearly 40 fold lower compared to the original rat mAb, the claims do not recite and therefore do not require a particular affinity. Thus, even if

variants have reduced binding affinity, such variants are within the scope of the claims. Consequently, the fact that a humanized antibody has reduced binding affinity for the antigen does not undermine Applicants' position that the claims are not adequately described. Rather, the fact that the humanized antibody retains detectable binding affinity for the antigen corroborates Applicants' position that the claims are adequately described under 35 U.S.C. §112, first paragraph. Furthermore, the 1991 publication date of the Gussow *et al.* reference is more than 10 years prior to the date the earliest priority application was filed, and as described herein the knowledge in the art concerning antibody humanization, and antibody structure and function at the time the application was filed, was far greater than in 2002 than in 1991.

Fourth, with respect to the Pero et al. publication (US 2003/0105000) cited at page 17 of the Action, this reference describes differences in binding of SH2 containing Grb14 proteins to another protein (ErbB2) and peptide-phage sequences, not binding between antibodies and antigens. Thus, Pero et al. describes interactions of proteins with other proteins that are unrelated to antibody-antigen interactions. Furthermore, Applicants' claims are not directed to variant antigen sequences in the sense that the antibodies and antigen binding fragments bind to various antigens having different epitopes. In this regard, the claims recite that the antibody or antigen binding fragment specifically binds to an epitope of a polypeptide expressed by at least one of ASPC-1 (ATCC Accession No. CRL-1682), or BXPC-3 (ATCC Accession No. CRL-1687) cells, and wherein PM-2 antibody produced by a cell line deposited as DSM ACC 2600 specifically binds to said epitope of the polypeptide. Consequently, the Pero et al. publication (US 2003/0105000) is irrelevant to whether or not the claimed antibodies and antigen binding fragments are adequately described under 35 U.S.C. §112, first paragraph.

A proper analysis for written description under 35 U.S.C. §112, first paragraph is whether one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991); see, also, *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985). Possession is assessed from the viewpoint of one of ordinary skill in the art: "Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). The description needed to satisfy the requirements of 35 U.S.C. §112 "varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in

existence.....Since the law is applied to each invention in view of the state of the relevant knowledge, its application will vary with differences in the state of the knowledge in the field and differences in the predictability of the science....the law must take cognizance of the scientific facts." *Capon v. Eshhar*, 418 F.3d , 1349, 1357 (Fed. Cir. 2005), emphasis added. In sum, an adequate written description is a factual inquiry measured by one of ordinary skill in the art that varies with the nature and scope of the invention, taking into consideration the scientific and technologic knowledge in existence in the relevant field.

There is no requirement for an actual reduction to practice or disclosure of a specific number of examples within the scope of the claims to satisfy the written description requirement under 35 U.S.C. §112, first paragraph. Furthermore, "Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." *In re Angstadt*, 537 F.2d 498, 502-503 (CCPA 1976), *Utter v. Hiraga*, 845 F.2d 993, 998-99 (Fed. Cir. 1988). In this regard, "(1) examples are not necessary to support adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006). Consequently, actual reduction to practice or disclosure of soecific examples of antibodies or antigen binding fragments within the scope of the claims is not required to satisfy written description under 35 U.S.C. §112, first paragraph.

Here, the claims comply with the written description requirement under 35 U.S.C. §112, first paragraph. First, the claimed antibodies and binding fragments are defined structurally and functionally. In particular, the claimed antibodies and fragments bind to an epitope of a polypeptide to which PM-2 antibody produced by the cell line deposited as DSM ACC 2600 binds. Furthermore, members of antibody genus that bind to a common epitope typically share sequence homology, such as in CDR3 of heavy chain variable region. Thus, antibodies that bind to the same epitope as PM-2 antibody can be expected to inherently share sequence homology with SEQ ID NO:5 and/or SEQ ID NO:7. Further in this regard, antibodies and binding fragments of claims 112 to 116 and 120 to 122 specifically require a minimal amount of sequence identity to SEQ ID NO:5 and/or SEQ ID NO:7. Thus, the claimed antibodies and binding fragments share 1) a common structural relationship with SEQ ID NO:5 and/or SEQ ID NO:7 (sequence identity); and 2) a common functional relationship with PM-2 antibody, namely binding to the same epitope. Given the sequence

homology and functional (binding) characteristics shared between the claimed antibodies and binding fragments, the antibodies and binding fragments have well defined functional and structural features in common.

Second, the claimed antibodies and binding fragments bind to an epitope of a polypeptide that PM-2 antibody produced by a cell line deposited as DSM ACC 2600 binds, and the polypeptide is expressed by at least one of two of the specifically defined cell lines. Thus, the epitope of the polypeptide is defined in terms of 1) expression by at least one of two well defined human cell lines; and 2) binding to PM-2 antibody produced by cell line deposited as DSM ACC 2600. Thus, one of skill in the art would know, without having to know more about the identity of the epitope or polypeptide, antibodies and antigen binding fragments within the scope of the claims. For example, competition binding is a simple and routine technique known in the art at the time of the invention to verify that a given antibody or fragment binds to a polypeptide expressed by a cell. An antibody or fragment that competes for PM-2 binding to a polypeptide expressed by at least one of the specifically recited cell lines would be within the scope of the claims. Consequently, one of skill in the art needs no more information about epitope or polypeptide identity in order to know antibodies and antigen binding fragments within the scope of the claims.

Third, the knowledge and skill in the art in terms of antibody structure correlating with function at the time of the invention was high. Namely, the role of antibody heavy and light chain variable regions, particularly CDRs and FRs, in antigen binding was well understood by the skilled artisan at the time of the invention. The specification also discloses the role of antibody heavy and light chain variable regions in antigen binding. Consequently, the level of knowledge and skill in the art with respect to antibody structure (CDRs, FRs, D- and J-regions, etc.) correlating with function was high at the time of the invention. Furthermore, the specification discloses antibody variable light and heavy chain region sequences (e.g., SEQ ID NOs:5 and 7), the predicted sequences and positions of all CDRs (Figures 14 and 15), and therefore also the location of the FRs. Consequently, the skilled artisan would know the predicted locations and amino acid sequences of all CDRs and FRs of SEQ ID NOs:5 and 7 that contribute to antigen binding.

Because the knowledge and skill in the art in terms of antibody structure correlating with function was high and the predicted location and sequences of CDRs and FRs in SEQ ID NOs:5 and 7 that contribute to antigen binding are disclosed, the skilled artisan would also have known residues in SEQ ID NOs:5 and 7 amenable to substitution. For example, in view

of the understanding of the role of CDRs and FRs in antigen binding at the time of the invention, the skilled artisan would know that an amino acid substitution, such as a conservative substitution, insertion or a deletion, for example, outside of a CDR or FR region of in SEQ ID NOs:5 and 7 would likely not destroy antigen binding activity. Furthermore, because of the high level of knowledge and skill in the art with respect to antibody structure correlating with function at the time of the invention one skilled in the art could have predicted with a high degree of confidence many substitutions of SEQ ID NOs:5 and 7 that would not destroy binding activity. Moreover, as discussed in detail below and evidenced by previously submitted Exhibits A-D (filed on September 30, 2008, in support of the Response to Office Action mailed March 31, 2008), substitutions or deletions/insertions of a limited number of amino acids within antibody CDRs (i.e., CDR1, CDR2 or CDR3) and FRs would be known to one of skill in the art to be tolerated.

The facts underlying the claimed antibodies and binding fragments are therefore analogous to the facts underlying *Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052 (Fed. Cir. 2005), in which the court held that a single embodiment of a protein (a reverse transcriptase (RT)) provided an adequate written description for claims directed to a genus of such proteins since the single disclosed protein embodiment had 1) sufficient correlation between structure and function; and 2) shared significant homology with others. In affirming that the patent claims satisfied the written description requirement, as articulated in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (1997) and *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993), the court held that "the shared written description for the patents-in-issue recites both the DNA and amino acid sequences of a representative embodiment of the claimed RT enzyme. The specification also discloses test data that the enzyme produced by the listed sequence has the claimed features—DNA polymerase activity without RNase H activity. Under both the *Eli Lilly* and *Fiers* analysis, the specification at bar is sufficient. In short, there is no error in the district court's ruling that the claims in the patents-in-suit satisfy the written description requirement of §112." Thus, the claims of the patents-in-issue in *Invitrogen*, which did not recite a particular amount of homology or identity to a reference sequence in the claims, satisfied the written description requirement even though there was only a single disclosed embodiment in the specification. In view of *Invitrogen*, a single embodiment provides an adequate written description of a genus of proteins where there is sufficient correlation between protein structure and function, and the members of the species share significant homology.

Here, given the substantial understanding of antibody structure correlating with function at the time of the invention, and that the specification discloses light and heavy chain variable region sequences including predicted positions and sequences of all CDRs and the location and sequences of all FRs, all sequences that mediate antigen binding would be known to one of skill in the art, and therefore regions amenable to variation would also be known. The claimed antibodies and binding fragments also share common structural (sequence homology) with reference sequences (SEQ ID NOs:5 or 7) and functional characteristics (bind to the epitope to which PM-2 antibody produced by a cell line deposited as DSM ACC 2600 specifically binds). Consequently, the underlying facts of the claims under consideration closely parallel the facts underlying the *Invitrogen* decision.

The Patent Office cites *Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004) at page 18 to support the rejection. However, the facts and context of the claims under consideration are distinguishable from those that led to the *Noelle* decision.

First, the claimed antibodies in *Noelle v. Lederman* were not directed to antibodies and antigen binding fragments that bind to the same epitope. Rather, *Noelle's* claims were directed to antibodies that bind to the mouse CD40CR antigen, and antibodies that bind to the human CD40CR antigen, and therefore include antibodies that bind to different epitopes on different polypeptides of different animal species. In contrast, the claimed antibodies and antigen binding fragments specifically bind to an epitope of a polypeptide expressed by at least one of two human cells, namely ASPC-1 (ATCC Accession No. CRL-1682), or BXPC-3 (ATCC Accession No. CRL-1687), wherein PM-2 antibody produced by a cell line deposited as DSM ACC 2600 specifically binds to said epitope of the polypeptide. Thus, in contrast to the antibodies claimed by *Noelle*, Applicants' claimed antibodies and antigen binding fragments all specifically bind to a single epitope of a polypeptide expressed by a well characterized human cell line.

Second, *Noelle* did not disclose a human CD40CR antigen. Thus, the court held that due to *Noelle*'s failure to describe human CD40CR antigen, that claims directed to antibodies that bound to an unknown antigen were not adequately described in view of the mouse CD40CR antigen. In contrast to *Noelle*, the claimed antibodies and antigen binding fragments bind to an epitope expressed by at least one of two well defined deposited human cell lines, and bind to an epitope of a polypeptide to which PM-2 antibody produced by a cell line deposited as DSM ACC 2600 specifically binds. Thus, in contrast to *Noelle* which did not describe the antigen to which the antibodies bind, Applicants' claimed antibodies and

antigen binding fragments bind to the epitope of a polypeptide expressed by at least one of two well defined deposited human cell lines, and by binding to the PM-2 antibody produced by the cell line deposited as DSM ACC 2600.

In sum, unlike *Noelle v. Lederman*, the claimed antibodies and antigen binding fragments 1) specifically bind to a single epitope expressed by at least one of two well defined deposited human cell lines; and 2) bind to an epitope of a polypeptide defined by expression by at least one of two well defined deposited human cell lines, and by binding to the PM-2 antibody. Consequently, the facts and context underlying Applicants' claims are clearly distinct from the facts and context in the *Noelle v. Lederman* decision and, therefore, the *Noelle* decision is inapposite.

The Patent Office also cites *In re Alonso*, 545 F.3d 1015 (Fed. Cir. 2008) at page 19 to support the rejection. However, *In re Alonso* is inapposite to the claims of this application because the facts and context underlying the claims under consideration are highly distinguishable from those that led to the *In re Alonso* decision.

First, the *Alonso* claims are directed to methods of treating neurofibrosarcomas, using antibodies idiotypic to the neurofibrosarcomas. Significantly, the antibodies in *Alonso* were not limited to binding to any particular epitope or any particular antigen. Instead, the genus of antibodies encompassed by the *Alonso* claims could bind to any epitope and any antigen expressed, which epitopes and antigens had different and unknown specificities. Thus, the claimed treatment methods of *Alonso* encompassed antibodies not limited to binding to any particular epitope or any particular antigen.

In contrast to the antibodies of *Alonso*, the claimed antibodies and antigen binding fragments all specifically bind to a single epitope, namely the epitope of a polypeptide expressed by at least one of two well defined neoplastic human cell lines recited in the claims to which the PM-2 antibody produced by a cell line deposited as DSM ACC 2600 specifically binds. Also in contrast to *Alonso*, the claimed antibodies and fragments bind to a polypeptide expressed by at least one of two well defined deposited human cell lines, namely ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cells.

Second, the antibodies in *Alonso* were not defined by or limited to any structure. In contrast to the *Alonso* antibodies, the claimed antibodies and antigen binding fragments share a common structure due to 1) binding to the same epitope; and 2) claims 112 to 116 and 120 to 123 specifically recite required amounts of sequence identity to light and heavy chain

variable regions (SEQ ID NOs:5 and 7). Thus, the claimed antibodies and fragments share a common structure (amino acid residues) owing to binding to the same epitope, and as specifically recited in claims.

The relevance of such claimed structure is illustrated by Xu and Davis (Immunity 13:37 (2000)), submitted herewith as Exhibit 1, who reported that CDR3 of the heavy chain variable region was the primary determinant which confers antigen recognition and specificity. Consequently, the claimed antibodies and binding fragments will have a CDR3 heavy chain variable region with significant sequence identity to CDR3 of SEQ ID NO:7, whereas in *Alonso* there was no structural relationship among the genus of antibodies.

Third, the patent application at issue in *Alonso* (USSN 08/469,749) claimed priority to an application filed in 1988. In contrast, the subject application claims priority to applications filed July 4 and 6, 2002, which is at least 13 years after the *Alonso* priority application was filed. Obviously, the state of knowledge in the art concerning antibody structure correlating with function was greater in 2002 than in 1988. Indeed, the state of the art was so much more advanced in 2002 that a finding based upon the state of the art in 1988 is wholly insufficient to make a factual evaluation of an invention in 2002. As an example of the advanced state of the art, in 1992, a publication reported substitutions of framework residues of humanized antibodies with donor framework residues improved antibody affinity (Foote and Winter, J. Mol. Biol. 224:487 (1992), submitted herewith as Exhibit 2) indicating that FR residue substitutions are tolerated and can improve affinity. As another example of the advanced state of the art, two publications, in 1998 and 2000, reported that CDR3 of heavy chain variable region was the principal determinant of antigen recognition and specificity (Exhibit 1; see, also, Morea et al. J. Mol. Biol. 275:269 (1998), submitted herewith as Exhibit 3). In particular, the authors of Exhibit 1 reported that changes in heavy chain CDR3 amino acids accounted for the diversity of response against various protein antigens, which did not require changes to CDR1 or CDR2 sequences, indicating that one of skill in the art would have known that heavy chain CDR1 and CDR2 are less important for antigen specificity compared to heavy chain CDR3. As yet another example of the advanced state of the art, a review publication by Padlan (Molecular Immunology 31:169 (1994), submitted herewith as Exhibit 4) report the role of FRs and CDRs in antibody function, that FRs have conserved substitutions (e.g., page 177), that CDR3 has a primary role in antigen specificity (page 196 second column), and that particular amino acid residues are more prevalent in CDRs/FRs (pages 197-198). Still another publication evidencing the advanced state of the art

reported the construction of a fully human combinatorial antibody library based upon human consensus FRs and CDRs (Knappik et al., J. Mol. Biol. 296:57 (2000) submitted herewith as Exhibit 5). Consequently, one of skill in the art would know antibody sequence regions more or less amenable to substitution, the types of amino acid residues that are most prevalent and/or tolerated at given positions and could therefore deduce binding variants based upon this knowledge.

A further example of the advanced state of the art is a publication by Collet *et al.* (Proc. Nat'l. Acad. Sci. USA 89:10026 (1992), submitted herewith as Exhibit 6), who reported that heavy chain variable region sequences could productively pair with a variety of different light chain variable region sequences and maintain antigen binding specificity (see, e.g., the abstract of Exhibit 6, which states that a heavy chain could productively pair with a light chain and still maintain HIV gp120 antigen binding activity from 43% -100%). Even unrelated light chain variable region sequences (to tetanus toxoid) productively paired with a heavy chain variable region sequence (to HIV gp120) to produce an antibody that maintained binding to HIV gp120 with a high degree of frequency (Exhibit 6, page 10029-10030). Thus, one of skill in the art would have known that the heavy chain variable region sequence can productively pair with a number of light chain variable region sequences and retain antigen specificity, indicating that variations to the light chain variable region sequence are tolerated.

Thus, the knowledge in the art concerning antibody structure correlating with function was significantly greater in 2002 than in 1988. Consequently, in view of the high level of knowledge and skill in the art, one of skill in the art would have been able to reasonably predict with a high degree of confidence variants of SEQ ID NO:5 and 7 that would retain binding.

Furthermore, in view of the fact that the claimed antibodies and fragments specifically bind to a single epitope and share a common structure, unlike the *Alonso* antibodies, and that the state of the art at the time of that the application was filed was more advanced as compared to the state of the art of the application at issue in *Alonso*, the claims under consideration are highly distinguishable from the *Alonso* decision.

Lastly, but significantly, the Appellants in the *Alonso* decision failed to timely present the argument that the neurofibrosarcoma antibodies were adequately described in view of the well-known correlation between structure and function of antibodies. Thus, the *Alonso* court did not even consider the merits of this argument since it was not raised during proceedings before the Board. Consequently, given the fact that arguments pointing out the well-known

correlation between structure and function of antibodies were not considered by the *Alonso* court, the *Alonso* decision expressly does not stand for the proposition that antibodies are not adequately described in spite of well-known correlation between structure and function of antibodies, particularly given the advances in the state of the art in the 14 years after the *Alonso* priority application was filed.

In sum, a proper analysis of the description requirement under 35 U.S.C. §112, first paragraph, requires a factual inquiry and consideration of the state of the knowledge in the relevant field. Here, the facts of the claimed antibodies and antigen binding fragments are readily distinguishable from *Alonso*. Namely, unlike *Alonso*, the claimed antibodies and fragments 1) specifically bind to a single epitope expressed by at least one of two well-defined deposited human cell lines; 2) share a common sequence structure due to binding to a single epitope and as specifically recited in claims 112 to 116 and 120 to 122; and 3) unlike *Alonso*, the knowledge in the art concerning antibody structure correlating with function was far more advanced in 2002 than in 1988, the priority date of the *Alonso* application. Furthermore, in reaching its decision the *Alonso* court failed to consider the well-known correlation between structure and function of antibodies.

Additionally, the accompanying Declaration under 37 C.F.R. §1.132 executed by Dr. Peter Vollmers verifies that the claims are adequately described under 35 U.S.C. §112, first paragraph. Dr. Vollmers provides objective facts, and conclusions based upon the objective facts, in the accompanying Declaration.

In terms of antibodies and binding fragments that comprise a light chain variable region sequence at least 75% identical to SEQ ID NO:5 and a heavy chain variable region sequence at least 75% identical to SEQ ID NO:7, Dr. Vollmers declares and states at paragraphs 6 to 15 of the Declaration that:

One skilled in the art, in view of the guidance of the specification and the knowledge and skill in the art concerning antibody structure and function at the time of the invention, would be apprised of a number of antibodies and antigen binding fragments that specifically bind to a polypeptide expressed by at least one of the recited cell lines, and (i) that comprise a light chain variable region sequence at least 75% identical to SEQ ID NO:5, and comprise a heavy chain variable region sequence at least 75% identical to SEQ ID NO:7; (ii) that comprise a light chain variable region sequence at least 80% identical to SEQ ID NO:5, and comprise a heavy chain variable region sequence at least 80% identical to SEQ ID NO:7; (iii) that comprise a light chain variable region sequence at least 85% identical to SEQ ID NO:5,

and comprise a heavy chain variable region sequence at least 85% identical to SEQ ID NO:7; (iv) that comprise a light chain variable region sequence at least 90% identical to SEQ ID NO:5, and comprise a heavy chain variable region sequence at least 90% identical to SEQ ID NO:7; or (v) that comprise a light chain variable region sequence at least 95% identical to SEQ ID NO:5, and comprise a heavy chain variable region sequence at least 95% identical to SEQ ID NO:7.

Dr. Vollmers' conclusions are based upon the following objective facts: The specification discloses the light chain variable region amino acid sequence, SEQ ID NO:5, and heavy chain variable region amino acid sequence, SEQ ID NO:7. The specification discloses that light and heavy chain variable region sequences SEQ ID NOs:5 and 7 are derived from a human antibody (Example 2). The specification also discloses the predicted sequence of all three CDRs in both variable region sequences (see, for example, Figures 14 and 15, page 5, lines 6-7 and 24-25, and page 50, lines 20-25). Dr. Vollmers therefore concludes that the skilled artisan would know the sequence and the predicted locations of the three CDRs in light and heavy chain variable regions, SEQ ID NOs:5 and 7.

Dr. Vollmers' furthermore declares that as the predicted locations of the three CDRs in SEQ ID NOs:5 and 7 would be known to the skilled artisan, the skilled artisan would also have known the location of the framework regions (FRs) in SEQ ID NOs:5 and 7, as well as the D- and J-regions in SEQ ID NOs:5 and 7. Dr. Vollmers therefore declares that the skilled artisan would know the sequence and location of amino acid residues of SEQ ID NOs:5 and 7 that contribute to antigen binding.

Dr. Vollmers declares that the level of knowledge and skill in the art concerning antibody structure and function at the time of the invention was high. As evidence of the high level of knowledge and skill in the art, the specification discloses the function of antibody heavy and light chain variable (e.g., CDR and FR) and constant regions (page 22, line 6, to page 23, line 2). The role of variable region sequences, including CDRs in antigen binding was known in the art at the time of the invention (see, for example, Immunology, Goldsby, R.A., 5th ed. W.H. Freeman, 2002).

Dr. Vollmers also declares that because the amino acids of light and heavy chain variable region sequences SEQ ID NOs:5 and 7 that contribute to antigen binding would be known to one of skill in the art in view of the specification and the high level of knowledge and skill in the art concerning antibody structure and function, the skilled artisan would have known a number of antibodies and functional fragments with amino acid residues of SEQ ID

NOs:5 and 7 that could be substituted (i.e., would likely not destroy binding activity). Consequently, the skill artisan would envision light chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:5, and heavy chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:7 that would have at least partial binding activity.

Dr. Vollmers illustrates the foregoing by way of the example of an amino acid substitution. In brief, an amino acid substitution such as a non-conservative or conservative substitution outside a CDR or FR region of SEQ ID NOs:5 or 7 would likely not destroy binding activity of an antibody, and conservative substitutions within a CDR or FR region of SEQ ID NOs:5 or 7 would also likely not destroy binding activity of an antibody or antigen binding fragment. Dr. Vollmers thus declares that the skilled artisan would know of a number of antibodies and antigen binding fragments comprising SEQ ID NO:5 or 7 with non-conservative or conservative substitutions located outside of a CDR or FR of SEQ ID NO:5 or 7, or conservative substitutions within a CDR or FR of SEQ ID NO:5 or 7, that likely retain at least partial binding activity (paragraph 10).

Dr. Vollmers points out that typically about half of the amino acids in a given heavy or light chain variable region sequence is not within one of the three CDRs. Dr. Vollmers concludes that because there are a large number of amino acids outside of the CDRs, the skilled artisan would envision a number of residues outside of CDRs that could be substituted and likely retain at least partial binding activity. Thus, Dr. Vollmers declares that the skilled artisan would readily envision antibodies and antigen binding fragments with light chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:5, and heavy chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:7, that would retain at least partial binding activity without actually having to verify that the variant has at least partial binding activity (paragraph 11).

Dr. Vollmers further declares that not only would the skilled artisan envision antibodies and antigen binding fragments with light chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:5, and heavy chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:7, that retain at least partial binding activity, but would also know of nonfunctional variants. For example, the skilled artisan knows that heavy chain variable region CDR3 appears to confer fine binding specificity, and therefore that a large number of

non-conservative substitutions, insertions or deletions of heavy chain variable region CDR3 would likely result in loss of antigen specificity. Dr. Vollmers therefore concludes that the skilled artisan would also know of SEQ ID NOs:5 and 7 with sufficient substitutions, insertions or deletions such that the antibody or functional fragment would be unlikely to have binding activity (paragraph 12).

Dr. Vollmers moreover declares that the ability of the skilled artisan to envision sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:5 and sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:7 that would retain at least partial binding activity is further evidenced by the fact that humanizing antibodies was known at the time of the invention (see, for example, U.S. Patent No. 6,180,370). In particular, Dr. Vollmers points out that grafting non-human CDRs to human framework sequences to form an antigen binding antibody was well established at the time of the invention. Dr. Vollmers concludes that because all CDRs of a given variable region sequence could be transferred from one mammalian species to another without destroying binding activity of the resultant antibody, the skilled artisan would readily envision antibodies and antigen binding fragments could comprise CDRs of one species and fragments of another without destruction of antigen binding activity that comprise light chain variable region sequences with 75% or more identity to SEQ ID NO:5, and heavy chain variable region sequences with 75% or more identity to SEQ ID NO:7. Moreover, Dr. Vollmers concludes that given that humanized antibodies retain binding and that variable region sequences can include non-identical amino acids in many positions outside of the CDRs without destroying binding activity, variants can be substantially non-identical to SEQ ID NOs:5 and 7 outside of the CDRs while retaining binding activity. Dr. Vollmers thus concludes that the skilled artisan would readily envision a number of antibodies and antigen binding fragments that vary in positions outside of the CDRs of SEQ ID NOs:5 and 7 that retain at least partial binding activity (paragraph 13).

To illustrate that substitutions within CDRs are tolerated, Dr Vollmers refers to Kipriyanov *et al.* (Protein Engineering 10:445 (1997), previously submitted as Exhibit A, on September 30, 2008, in support of the Response to Office Action mailed March 31, 2008) who report that a substitution of a cysteine residue by a serine within CDR3 of an antibody heavy chain variable region did not have an adverse effect on binding affinity. Thus, previously submitted Exhibit A corroborates that the skill artisan would know that a

substitution of a light or heavy chain variable region CDR residue are tolerated and would not necessarily destroy binding activity (paragraph 14).

To illustrate that substitutions within FRs can generally be tolerated, Dr. Vollmers refers to Holmes *et al.* (J. Immunol. 167:296 (2001), previously submitted as Exhibit B on September 30, 2008, in support of the Response to Office Action mailed March 31, 2008), who report that several heavy chain variable region FR substitutions of an anti-lysozyme antibody did not destroy binding activity. Thus, Dr. Vollmers concludes that antibodies and antigen binding fragments with a substitution of a light or heavy chain variable region FR residue are tolerated and would not destroy binding activity (paragraph 15).

Concerning antibodies and antigen binding fragments that comprise a light chain variable region sequence at least 75% identical to SEQ ID NO:5 and a heavy chain variable region sequence at least 75% identical to SEQ ID NO:7, wherein the light or heavy chain variable region sequence has an insertion or deletion of one amino acid residue, Dr. Vollmers declares and states at paragraphs 16 to 19 of the Declaration that:

One skilled in the art, in view of the guidance of the specification and the knowledge and skill in the art concerning antibody structure and function at the time of the invention, would be apprised of a number of antibodies and antigen binding fragments that specifically bind to a polypeptide expressed by at least one of the recited cell lines and that comprise a light chain variable region sequence at least 75% identical to SEQ ID NO:5 and a heavy chain variable region sequence at least 75% identical to SEQ ID NO:7, wherein the light or heavy chain variable region sequence has an insertion or deletion of an amino acid residue (paragraph 16).

Dr. Vollmers' conclusions are based upon the following objective facts: again, the sequence of amino acid residues of light and heavy chain variable region sequences SEQ ID NOs:5 and 7 and corresponding CDRs, FRs, etc., that contribute to antigen binding would be known, and the level of knowledge and skill in the art concerning antibody structure and function was high. Consequently, the skilled artisan would have known antibodies and fragments with substitutions of SEQ ID NOs:5 and 7 that would not destroy binding activity, and therefore would envision variable region sequences with 75% or more identity to SEQ ID NO:5 and 7 (e.g., 80%, 85%, 90%, 95%, etc.) with at least partial activity. In addition, an amino acid insertion or deletion of SEQ ID NOs:5 or 7 would also likely not destroy binding activity of an antibody (paragraph 18).

To corroborate the foregoing conclusions concerning insertions and deletions of amino acid residues in heavy and light chain variable regions, including CDRs, Dr. Vollmers points out that such alterations occur during antibody affinity maturation, and refers to Wilson *et al.* (J. Exp. Med. 187:59 (1998) previously submitted as Exhibit C on September 30, 2008, in support of the Response to Office Action mailed March 31, 2008), whom report a number of insertions and deletions of variable heavy chains that occur naturally during affinity maturation. Dr. Vollmers therefore concludes that the skilled artisan would know with a high degree of confidence that an antibody or antigen binding fragment comprising SEQ ID NO:5 or 7 with an amino acid insertion or deletion within or outside of a CDR, would very likely retain at least partial binding activity.

To further corroborate Dr. Vollmers' conclusions that antibodies and antigen binding fragments with a light or heavy and chain variable region sequence insertion or deletion can be tolerated, even within a CDRs, he refers to Lantto and Ohlin (J. Biol. Chem. 277:45108 (2002), previously submitted as Exhibit D on September 30, 2008, in support of the Response to Office Action mailed March 31, 2008), whom report that single amino acid insertions or deletions of CDRs 1 and 2 of heavy chain variable region of an antibody were well tolerated. Thus, Exhibits C and D corroborate that antibodies and antigen binding fragments that comprise a light or heavy chain variable region sequence insertion or deletion, even within a CDR, can be tolerated (paragraph 19).

In sum, given the totality of: guidance in the specification and the high level of knowledge and skill in the art with respect to antibody structure correlating with function at the time of the invention, knowledge of the light and heavy chain variable region sequences (SEQ ID NOs:5 and 7) and the CDRs and FRs that confer binding, and as also corroborated by the Declaration under 37 C.F.R. §1.132 executed by Dr. Vollmers submitted herewith and previously submitted Exhibits A-D, the skilled artisan would know of general regions and particular residues that would be amenable to variation and would therefore be apprised of a number of sequence variants of SEQ ID NOs:5 and 7 having binding activity, the claims meet the written description standard articulated by the court in *Invitrogen*. Further in view of the substantially greater understanding of antibody sequence structure and correlation with function in 2002 compared to 1988, and that the claimed antibodies and fragments will bind to a single identical epitope, namely the epitope to which the PM-2 antibody comprising SEQ ID NOs:5 and 7 binds, and will also necessarily have sequence homology with SEQ ID NOs:5 or 7, the facts of the claims under consideration are clearly distinguishable from the

facts in *Alonso*. Consequently, the claims are adequately described under 35 U.S.C. §112, first paragraph, and the rejection must be withdrawn.

II. REJECTION UNDER 35 U.S.C. §102(b)

The rejection of claims 111 and 124 to 130 under 35 U.S.C. §102(b) as allegedly anticipated by Overholser *et al.* (Cancer 89:74 (2000)) as evidenced by US Patent No. 6,794,494 (Young *et al.*) is respectfully traversed. Allegedly, Overholser *et al.* describe an antibody, IMC-225 that binds to EGFR expressed by BXPC-3 cells, and Young *et al.* describe antibody c225 that binds EGFR in CACO-2 cells, as set forth on page 23 of the Office Action.

Claims 111 to 122 and 126 to 130 are not anticipated by Overholser *et al.* (Cancer 89:74 (2000)). In this regard, as discussed above, the claims do not encompass "a genus of antibodies binding to unknown epitopes on unknown proteins," but are directed to antibodies and antigen binding fragments that specifically bind to the epitope that the PM-2 antibody specifically binds. In addition, the claimed antibodies and fragments bind to an epitope of a polypeptide having an approximate molecular weight of 115 kDa. Overholser *et al.* fail to describe such antibodies or antigen binding fragments. Consequently, Overholser *et al.* fail to anticipate claims 111 to 122 and 126 to 130 and Applicants respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that the claims clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065. Please charge any fees associated with the submission of this paper to Deposit Account Number 033975. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully submitted,

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